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EFFECT OF IONIZING RADIATION ON SHOCK-ELICITED AGGRESSION OF MALE RATS

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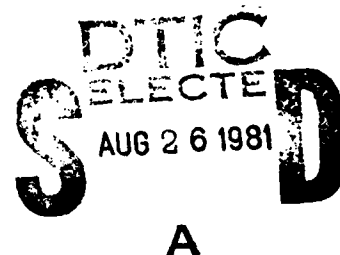
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
Several pairs of male Sprague-Dawley rats were exposed to either 0, 350, 700, 1400, or 2100 rads of Co^{60} radiation at 250 rads/min. Pairs were then tested for aggression at 20 min, 6 h, 24 h, 72 h, and 7 d post irradiation. Each test session lasted for 5 min and consisted of 50 3-W shocks of 0.5-s duration with a 5.5-s shock-shock interval. Scores indicated how many aggressive interactions took place during the 50 intershock intervals. Aggressive interactions in the 700-rad group increased ($p < .025$) at 72 h post irradiation. Secondarily, to validate the experimental procedure, a known aggression-reducing drug was tested

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20. ABSTRACT (Continued)

on a different set of rats. Chlorpromazine hydrochloride, 2 mg/kg, intramuscular, caused a decrease in aggression 120 min post injection ($p < .01$).

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EFFECT OF IONIZING RADIATION ON SHOCK-ELICITED AGGRESSION
OF MALE RATS

INTRODUCTION

Investigators have reported conflicting relationships between neurotransmitters and aggression. There are several different tests of animal aggression as well as different motivations for aggression, and neurotransmitters may play different roles in different situations. Predatory aggression is facilitated by 5-hydroxytryptamine (5-HT) depletion, irritable aggression (shock motivated) is altered by modifications in norepinephrine (NE) levels, and spontaneous aggression appears to be related to stimulation of dopamine (DA) metabolism (1). In three related studies (1-3), shock-elicited aggression increased as a result of decreases in NE. It was hypothesized that decreases in NE caused an increase in activity of the NE receptor by making the receptor hypersensitive and that this resulted in an increase in aggression. In an experiment examining mouse-killing rats (4), killer rats had 25.5% more NE in the forebrain than did non-aggressive animals.

Histamine also has been proposed as a neurochemical correlate to aggression (5). The histamine-releasing compound, 175-S, decreased aggression in monkeys but induced aggression in hamsters. Cyclohexylamine, also a histamine-releasing agent, decreased pain-elicited aggression in mice and aggression elicited by bilateral removal of the olfactory bulb in rats (6). These findings should lead to speculation that, in addition to considering different types of aggression, species and strain differences must be taken into account.

There is strong evidence that irradiation affects neurochemical levels. Again, different types of radiation may each operate in a different manner on chemical levels and structure. In the adult rat, noradrenalin and 5-HT decreased immediately after 900-rad X-ray treatment and continued to drop to their lowest levels by 24 h (7). Also, X-irradiation injured central monoamine (MA) terminals in the rat brain, but the damage was reversible (8). Monoamine oxidase (MAO) activity was markedly decreased in all brain areas studied after exposure to 18,000 rads of radiation rich in neutrons (9).

Very little research has been done on the effects of radiation on aggression, and we found no reports involving radiation effects on shock-elicited aggression. Mouse killing by rats was suppressed following pairings of mouse presentations (CS) with 96 R of ionizing radiation (US) at 0- and 30-min US-CS interstimulus intervals (10). McDowell et al. (11) observed decreased activity, object manipulation, and social aggression in rhesus monkeys (*Macaca mulatta*) immediately after irradiation and persisting long after. Mattsson and Yochmowitz (12) found that normally aggressive rhesus monkeys became very calm and showed minimal threat behavior after exposure to 450 rads of gamma radiation. This tranquil period began approximately 30 min after exposure and lasted 2-4 h. Sleeping was common during this period. When signs of sickness abated, the animals became alert and aggressive again, and except for anorexia, showed little or no evidence of having been irradiated. Dahlström et al. (8)

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observed a slight increase in handler-oriented aggression 24 h after 4000-R "head-only" radiation in Sprague-Dawley rats. After 7 d they displayed bursts of supranormal activity with jerks toward the edge of the cage and occasional outbursts towards the handler.

The studies just described indicate the following: (1) Changes in neurotransmitters such as DA, NE, and 5-HT are associated with changes in aggression; (2) irradiation causes a change in neurotransmitter levels; and (3) irradiation may cause changes in aggression. To objectively evaluate the effects of ionizing radiation on aggression, the following study determined the effects of 350 to 2100 rads Co^{60} gamma radiation on shock-elicited aggression of pairs of male rats at several postirradiation time intervals.

METHODS

Subjects

A total of 120 male Hilltop Sprague-Dawley rats, weighing between 250 and 450 g, were used in this experiment. Subjects were housed separately, and Purina Rat Chow and water were continuously available.

Apparatus and Procedure

The literature on shock-elicited aggression provided a great deal of information on manipulation of parameters such as shock intensity, shock duration, housing conditions, number of sessions, and temperature. In a study by Dreyer and Church (13), the number of fights increased with the intensity of shock from 0.5 to 2.0 mA, but higher intensities resulted in fewer fights because of increasing debilitation due to the shock. Dreyer and Church (13) and Azrin et al. (14) agree that longer shock time is directly related to increased fighting. For example, Azrin et al. (14) showed that 25% of the shocks elicited fighting at 0.075-s, 90% at 0.5-s, and 97% at 3.0-s duration. Intensity, however, seems to have a greater influence than duration (13). Housing conditions also seem to affect stability and rate of fighting. Shock-elicited fighting rates of rats housed in individual cages stabilized in fewer sessions than were required by animals that remained with the same partners both in the home cage and in the experimental chamber (15). In addition to housing conditions, another preexperimental parameter contributing to rate of fighting is the number of sessions required for stabilization. In an experiment by Powell et al. (16), the mean number of sessions required for stable fighting was 12.8, with a range of 7-18. Increasing ambient temperature from 40° to 100° F (4° to 36° C) also increases the probability of shock-elicited aggression in rats (17).

In this study we used a 29.0- x 23.5- x 19.5-cm Plexiglas box with aluminum rods spaced 1.23 cm apart; a shock generator equipped with scrambler (type SGS-001 from BRS division of TECH SERV, Inc.); a BRS PS-011 12-V, 18-A power supply; and BRS digibit control equipment and counters. Each daily session lasted 5 min and consisted of 50 trials, each initiated by a 3-W shock of 0.5-s duration delivered at 6-s intervals. The number of trials in which aggressive

interactions occurred between two randomly paired animals was recorded. Behavioral categories that constituted aggression were: (1) stand and orient (a orients to b), (2) touch, or (3) bite. A score was 1 if any of these occurred and 0 if none occurred.

Prior to irradiation Ss were isolated for 2 weeks in individual cages and then tested on each of 5 consecutive days to provide baseline data. Five groups of 12 pairs of rats were used in this study. Each group received either 0, 350, 700, 1400, or 2100 rads at 250 rads/min from a 9000-curie Eldorado 78 Co^{60} teletherapy unit. During irradiation Ss were placed in Plexiglas restraints. Following irradiation or sham exposure, pairs were tested after 20 min, 6 h, 24 h, 72 h, and 1 week. The 1400- and 2100-rad groups were euthanized after 24 h because the animals would have become overtly sick after that time.

For statistical analysis of the data, animal pairs that were aggressive more than 80% or less than 20% of the total session during the last 3 days of baseline were eliminated to avoid masking a radiation effect that might occur. For example, if radiation causes a decrease in aggression, but the animals are almost totally nonaggressive before radiation, a false reading of "no change" will occur since the data can go no lower. If radiation causes an increase in aggression, a similar argument can be used regarding animals whose baseline reading is too high. Postirradiation aggression was determined per animal pair by subtracting the average of the last three baseline scores from each postirradiation score.

A repeated-measurements analysis of variance was used to test for general differences among dose groups across time. Since we had some concern about meeting the assumption of normality required by the analysis, we decided to use two nonparametric procedures to check the results. Kruskal-Wallis H tests were used to compare the dose groups at each time separately. Also, Friedman's two-way analyses of ranked data were used to test each dose group for differences across time. Friedman's tests were performed on the original data rather than on the baseline-to-post changes.

A question arose during the study as to whether the shock-elicited aggression procedure could actually detect changes in aggression. To validate the procedure, we performed a second experiment using 24 new animals and a known aggression-reducing drug. Because of the available literature and amount of time chlorpromazine hydrochloride (Thorazine) has been in existence, it was considered the best drug to produce conclusive results. Two groups of six pairs of animals each were baselined for 4 d prior to being injected intramuscularly, and then tested 30 min and 2 h afterward. One group received 2 mg/kg of Thorazine (5 mg/ml), and the other received 0.9% saline solution. Statistical analysis consisted of (a) Friedman's two-way analyses of ranked data to test each group for differences across the entire time span and (b) Wilcoxon matched-pairs signed rank tests to test each group for specific differences between the lowest baseline and each postinjection time.

RESULTS

The results of the irradiation experiment were as follows. The repeated-measures ANOVA detected a significant group x time interaction (F (8,109) = 2.15, p <.05), and inspection indicated increased aggression in the 700 rad

group at 72 h (Fig. 1). The Kruskal-Wallis tests found group differences only at 72 h ($\underline{H}(2) = 7.65$, $\underline{p} < .05$), showing the same pattern. The Friedman tests further confirmed that only the 700-rad group displayed a significant change in aggression over time ($\chi_r^2 (7) = 14.32$, $\underline{p} < .05$). No other significant changes were detected by any of the tests.
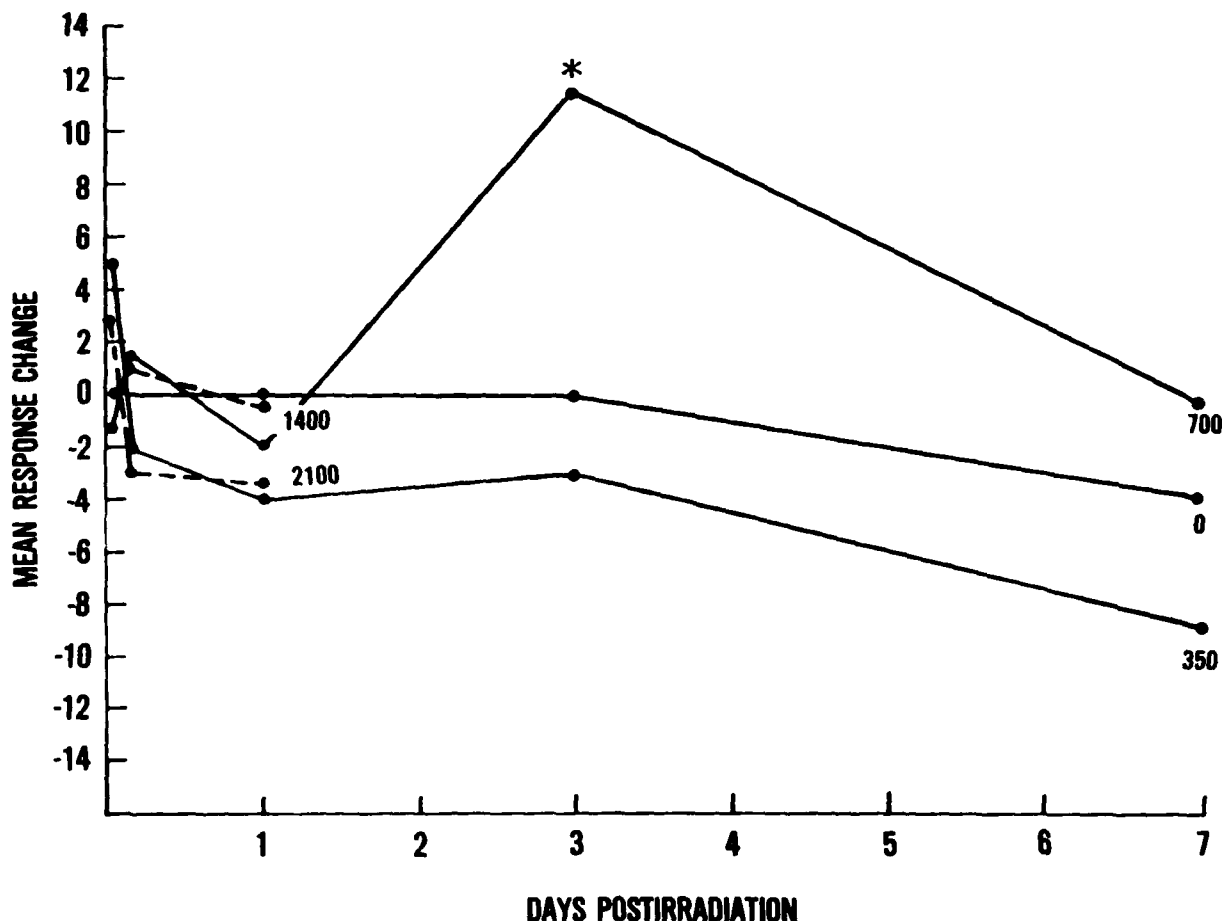
Figure 1. Baseline-to-postirradiation changes in aggressive interactions for all groups. *--Mean response change in aggression at 72 h after irradiation in the 700-rad group.

Figure 2 shows that variance associated with a comparison of two group means at any given time period was rather high (S.D. of differences between means = 10.1). Therefore, in comparing two groups, the power ($1-\beta$) of detecting a true difference of even moderate size would be fairly low in this experiment. In fact, the true difference between two groups would have to exceed 1.27 S.D., or 12.8 instances of aggression, just to have an 80% chance (power = .8) of detecting that difference. The true difference would have to exceed 1.46 S.D., or 14.7 instances of aggression, to have 90% power.

Figure 2. Power of detecting group differences in aggressive interactions
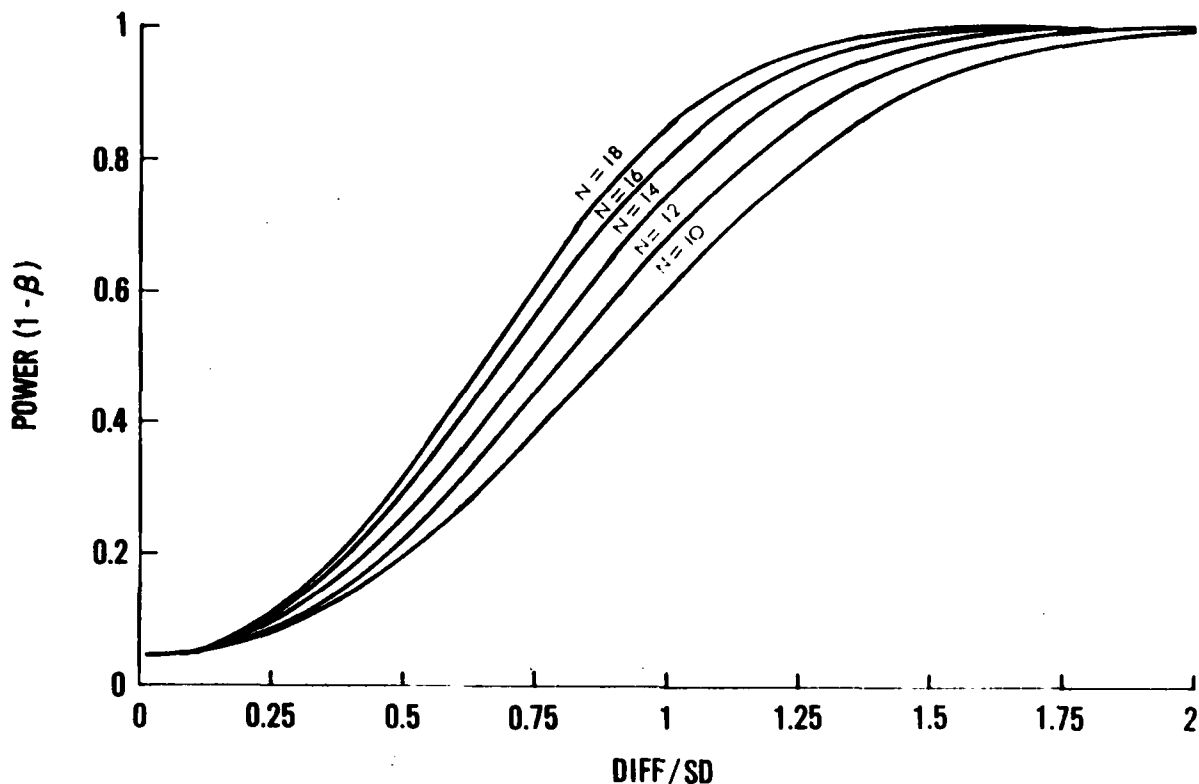for a given number of subjects.

The analysis of chlorpromazine data in Figure 3 showed differences over
time for the drug group, $\chi_r^2 (4) = 18.5$, $p < .01$, but no differences were found
in the saline control group. Further analyses by Wilcoxon matched-pairs
indicated a significant decrease at 120 minutes for the drug group, $I = 0$
(n=6), $p < .05$.

DISCUSSION

A general decrease in various postirradiation activity levels, which were
placed under the "fatigue" and "malaise" syndrome, has been reported from many
previous experiments (18,19). As already mentioned, irradiation and certain
drugs deplete NE and 5-HT, and varied behavioral syndromes occur as a result of
these depletions. The role of transmitters in aggression, or in other behaviors
for that matter, is exceedingly complex and involves relationships between
several neurotransmitter systems rather than endogenous levels of one isolated
system. For example, decreases in NE and 5-HT increased shock-elicited aggres-
sion, but lower NE levels decreased isolation-induced and predatory aggression
(20-23). Other behavioral changes, such as fewer initiated social inter-
actions, less physical activity, and a general inability to cope with environ-
mental stimuli, were attributed to decreased NE and DA levels (20,24-26).
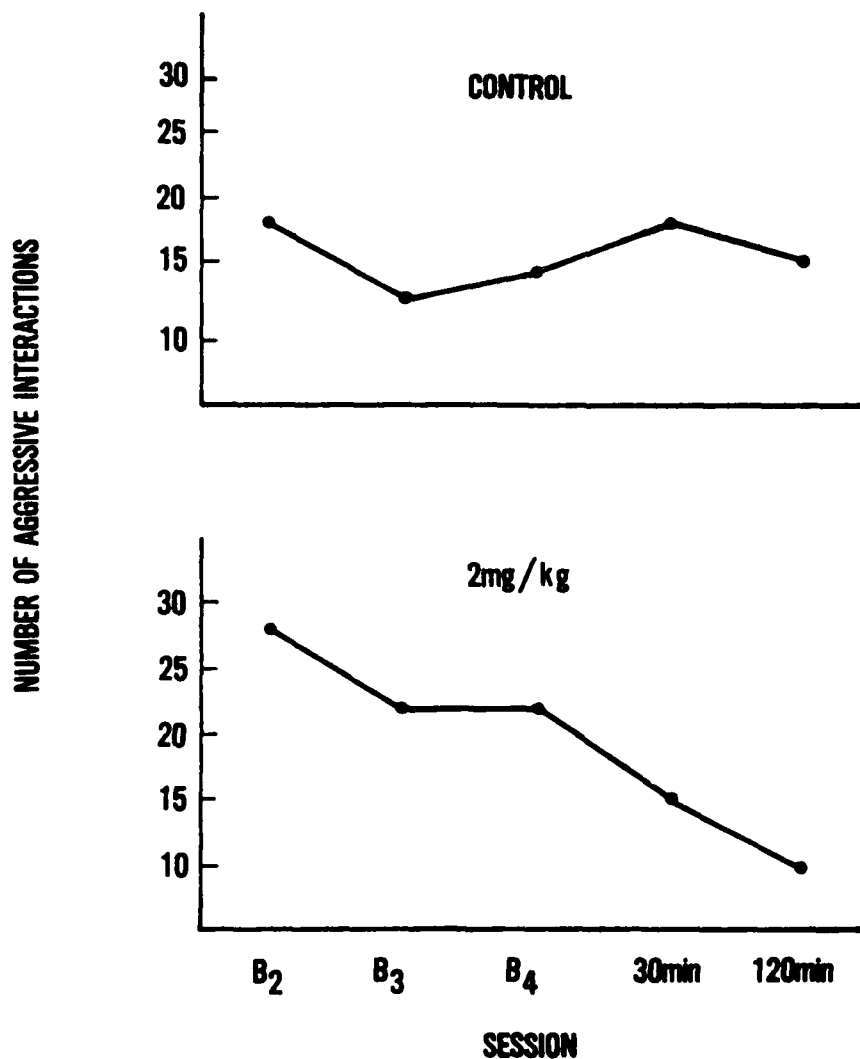
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Figure 3. Number of aggressive interactions before and
after injection of 2 mg/kg chlorpromazine
hydrochloride or 0.9% saline solution.

The seemingly contradictory findings from our experiment (increased aggression) as compared to findings from other experiments and observations (decreased aggression) may be explained in terms of task specificity.

Another problem which must be examined is the cyclic pattern of the behavior. In other words, why does aggression increase just at 72 h? Earlier studies using volitional and diffuse activity as a measure of performance after irradiation reveal that similar patterns exist, although not in the same time frame (27,28). More specifically, a delayed reaction at 72 h can be found in various physiological parameters. Weber and Steggerda (29) reported a gradual increase in assayable histamine starting the 2nd day after irradiation and continuing until the 5th day. If the rats survived this critical

4- to 6-day period and showed signs of recovery, no evidence of histamine was present in the blood by the 9th or 10th day. In another study, peripheral blood pressure in rats exposed to 970 R was much less responsive to intravenous injection of NE at 72 h through 96 h (30). Thoa et al. (2) reported a significant increase in shock-induced aggression and decrease in NE in the rat 4 d after an intraventricular injection of 90 mg of 6-hydroxydopamine. Parachlorophenylalanine, which effectively decreases synthesis of 5-HT, caused bizarre behavior in rats and cats, including increased aggression and increased sexual mounting orientation 4-5 days after treatment was started (31-34). An alternative explanation for the differences found in a shock-motivated task is that either an increase in histamine or a decrease in 5-HT appears to cause increased skin sensitivity (35-37). These phenomena might also explain the postirradiation increase in self-directed activity (whether by visual, manual, or oral response to S's own body) observed by McDowell et al. (11).

In conclusion, considerable evidence shows that ionizing radiation changes neurotransmitters and that changes in neurotransmitters occur simultaneously with changes in behavior. In this experiment, an increase in aggression occurred 72 h after exposure to 700 rads gamma irradiation. This is a complex phenomenon, however, and must be further investigated. Future investigations might include a sex-comparison study to evaluate the role of hormones such as testosterone and estrogen, which are linked to gender differences in radiation studies by Mickley (38). Also, experiments examining shock sensitivity, operant paradigms, different time intervals, territorial aggression, spontaneous aggression in groups, general physical activity, and biochemical changes should be considered.

REFERENCES

1. Eichelman, B. S., and N. B. Thoa. The aggressive monoamines. Biol Psychiatry 2(6):143-164 (1973).

2. Thoa, N. B., B. Eichelman, J. S. Richardson, and D. Jacobwitz. 6-Hydroxydopa depletion of brain norepinephrine and the function of aggressive behavior. Science 178:75-77 (1972).

3. Thoa, N. B., B. Eichelman, and L. K. Ng. Shock-induced aggression: Effects of 6-hydroxydopamine and other pharmacological agents. Brain Res 43:467-475 (1972).

4. Goldberg, M. E., and A. I. Salama. Norepinephrine turnover and brain monoamine levels in aggressive mouse-killing rats. Biochem Pharmacol 18:532-534 (1969).

5. Kido, R., K. Hirose, K. Yamamoto, and A. Matsushita. Effects of some drugs on aggressive behavior and the electrical activity of the limbic system. Prog Brain Res 27:365-382 (1967).

6. Miyata, T., Y. Kasé, Y. Kamikawa, M. Kataoka, K. Kikuchi, and T. Touchi. Pharmacological characteristics of cyclohexylamine, one of the metabolites of cyclamate. Life Sci 8:843-853 (1969).

7. Palaic, D. J., and Z. Supek. Liberation of brain 5-hydroxytryptamine and
    noradrenaline by X-ray treatment in the newborn and adult rat. J Neurochem
    13:705-709 (1966).

8. Dahlström, A., J. Häggendal, and B. Rosengren. The effect of roentgen
    irradiation on monoamine-containing neurons in the rat brain. Acta
    Radiol [Therapy] (Stockh) 12:191-200 (1973).

9. Catravas, G. N., and C. G. McHale. Changed activities of brain enzymes
    involved in neurotransmitter metabolism in rats exposed to different
    qualities of ionizing radiation. J Neurochem 24:673-676 (1975).

10. Boyle, M. Suppression of mouse killing in rats following irradiation.
    Percept Mot Skills 42:511-514 (1976).

11. McDowell, A. A., R. T. Davis, and J. P. Steele. Application of systematic
    direct observational methods to the analysis of the radiation syndrome
    in monkeys. Percept Mot Skills 6:117-130 (1956).

12. Mattsson, J. L., and M. G. Yochmowitz. Radiation-induced emesis in monkeys.
    Radiat Res 82:191-199 (1980).

13. Dreyer, P. L., and R. Church. Shock-induced fighting as a function of the
    intensity and duration of the aversive stimulus. Psychon Sci 10:271-272
    (1968).

14. Azrin, N. H., R. E. Ulrich, R. R. Hutchinson, and D. G. Norman. Effect of
    shock duration on shock-induced fighting. J Exp Anal Behav 7:9-11 (1964).

15. Creer, T. L., and D. A. Powell. Effects of age and housing conditions on
    shock-induced aggression. Psychon Sci 22:259-261 (1971).

16. Powell, D. A., K. Walters, S. Duncan, and J. R. Holley. The effects of
    chlorpromazine and d-amphetamine upon shock-elicited aggression.
    Psychopharmacologia 30:303-314 (1973).

17. Berry, M. B., and C. E. Jack. The effect of temperature upon shock-elicited
    aggression in rats. Psychon Sci 23:341-343 (1971).

18. Furchtgott, E. Behavioral effects of ionizing radiations. Psychol Bull
    53:321-334 (1956).

19. McDowell, A. A., and W. L. Brown. Running wheel activity of rats tested
    under varying conditions of food deprivation thirty-three days after
    acute exposure to 1,050 R of gamma radiation. School of Aviation Medicine,
    Air University, Report No. 58-143, Randolph AFB, Texas, Mar 1959.

20. Redmond, D. E., Jr., J. W. Mass, A. Kling, C. W. Graham, and H. Dekirmenjian.
    Social behavior of monkeys selectively depleted on monoamines.
    Science 174:428-431 (1971).

21. Baggio, G., and F. Ferrari. Role of brain dopaminergic mechanisms in
    rodent aggressive behavior: Influence of (±) N-n-propyl-norapomorphine
    on three experimental models. Psychopharmacology 70:63-68 (1980).

22. Avis, H. H. The neuropharmacology of aggression: A critical review. Psychol Bull 81:47-63 (1974).

23. Ellison, G. D., and D. E. Bresler. Tests of emotional behavior in rats following depletion of norepinephrine, or serotonin, or of both. Psychopharmacologia 34:275-288 (1974).

24. Bresler, D. E. Monamines and affect: A study of emotional behavior in rats depleted of catecholamines, serotonin, or both (Doctoral dissertation, University of California, Los Angeles, 1972). Dissertation Abstracts International, No. 73-1685, 33:3972-3973, 1973.

25. Ellison, G. D. Animal models of psychopathology. Am Psychol 32:1036-1045 (1977).

26. Antelman, S. M., and A. R. Caggiula. Norepinephrine-dopamine interactions and behavior. Science 195:646-653 (1977).

27. Jones, D. C., D. J. Kimeldorf, D. O. Rubadeau, G. K. Osborn, and T. J. Castanera. Effect of X-irradiation on performance of volitional activity by the adult male rat. Am J Physiol 77:243-250 (1954).

28. Castanera, T. J., D. C. Jones, and D. J. Kimeldorf. The effect of X-irradiation on the diffuse activity performance of rats, guinea pigs, and hamsters. Br J Radiol 32:386-389 (1959).

29. Weber, R. P., and F. R. Steggerda. Histamine in rat plasma; correlation with blood pressure changes following X-irradiation. Proc Soc Exp Biol Med 70:261-263 (1949).

30. Phillips, R. D., and D. J. Kimeldorf. The effect of whole-body X-irradiation on blood pressure in the rat. Radiat Res 18:86-95 (1963).

31. Ferguson, J., S. Henriksen, H. Cohen, G. Mitchell, J. Barchas, W. Dement. Hypersexuality and behavioral changes in cats caused by administration of p-chlorophenylalanine. Science 168:499 (1970).

32. Sheard, M. H. The effect of p-chlorophenylalanine on behavior in rats: Relation to brain serotonin and 5-hydroxyindoleacetic acid. Brain Res 15:524-528 (1969).

33. Shillito, E. E. The effect of parachlorophenylalanine. Br J Pharmacol 38:305 (1970).

34. Tagliamonte, A., P. Tagliamonte, G. L. Gessa, and B. B. Brodie. Compulsive sexual activity induced by p-chlorophenylalanine in normal and pinealectomized rats. Science 166:1433 (1969).

35. Douglass, W. W. Histamine and 5-hydroxytryptamine (serotonin) and their antagonist. In Goodman, L. S., and A. S. Gillman (eds.). The pharmacological basis of therapeutics (6th ed.). New York: MacMillan, 1975.

36. Conner, R. L., J. M. Stolk, and S. Levine. Effects of PCPA on fighting behavior and habituation of startle response in rats, pp. 325-333. In Barchas, J., and E. Usdin (eds.). Serotonin and behavior. New York: Academic Press, 1973.

37. Tenen, S. S. The effects of p-chlorophenylalanine, a serotonin depletor, on avoidance acquisition, pain sensitivity, and related behavior in the rat. Psychopharmacologia 10:204-219 (1967).

38. Mickley, A. M. Behavioral and physiological changes produced by a supralethal dose of ionizing radiation: evidence for hormone-influenced sex differences in the rat. Radiat Res 81:48-75 (1980).